REMARKS

Applicants have studied the Office Action mailed November 3, 2003 and have made amendments to the claims and specification. It is respectfully submitted that the application, as amended, is in condition for allowance. Reconsideration and allowance of the pending claims in view of the above amendments and following remarks is respectfully requested.

Sequence Compliance

The Examiner indicated that certain sequences presented in Figures 2A-2B and 3BB-3FF have not been identified by a sequence identifier.

Applicants are hereby submitting a Substitute Sequence Listing containing the relevant sequences which were previously absent from the Sequence Listing, along with Replacement Drawing Sheets which properly identify these sequences by sequence identifiers.

Specification/Informalities

The Examiner indicated that the attempt to incorporate subject matter into the application by reference to a hyperlink embedded in the specification is improper (p. 9, lines 26 and 30). Additionally, the Examiner indicated that the "Description of the Figure Sheets" section of the specification fails to properly identify the drawings.

Applicants have hereby amended the specification, as indicated above, to remove the hyperlinks from the specification. The hyperlinks were not needed for enablement of the invention, but merely provided additional background material.

Additionally, Applicants have amended the "Description of the Figure Sheets" section, as indicated above, to more accurately identify the drawings.

Corrections to third paragraph on page 3 of the specification

The third paragraph on page 3 of the specification has been amended, as indicated above, to correct the first named author in the *J Cell Biol* 2001 Jul 23;154(2):447-58 reference. This is the same reference that was cited by the Examiner in the Office Action

mailed November 3, 2003. The citation of this reference at the third paragraph of p. 3 of the specification erroneously named the second author (Schmidt) instead of the first author (Brandenberger).

Rejection of claims 4, 8-9, and 24-37 under 35 USC §101

The Examiner rejection claims 4, 8-9, and 24-37 as not being supported by either a specific and substantial asserted utility or a well-established utility. In summary, the Examiner asserts that the claimed polynucleotide has no substantial utility as further experimentation is required to establish its "real world" use. The Examiner states that the specification fails to provide the necessary guidance such that one of ordinary skill in the art could obtain the desired therapeutic effect, i.e., treating developmental disorders and, thus, further experimentation is required in order to identify those agents that may be useful in targeting nephronectin and the type of developmental disorders that may be treated with such. The Examiner further states that one of ordinary skill in the art would recognize that further experimentation is required to establish a "real world" use for the polynucleotide of SEQ ID NO:1 or 3 and the recited variants thereof, and this type of utility is not considered a "substantial utility". The Examiner states that here the claimed polynucleotides are suitable only for additional research. Further, the Examiner states that the specification fails to disclose a nexus between the claimed polynucleotides and a specific disease state such that the polynucleotide is useful as a diagnostic or in the treatment of a disease state or condition; therefore, the asserted utilities are not specific to the claimed polynucleotides and are instead general utilities that would be applicable to the broad class of polynucleotides. The Examiner concludes that the claimed polynucleotide has no specific and substantial utility.

In response, Applicants respectfully assert that nephronectins like the nephronectin encoded by the claimed polynucleotides are supported by specific and substantial utilities related to the treatment (and/or diagnosis) of developmental disorders, as indicated on page 3 of the specification. This is indicated in the specification, and has also been established in the art, particularly by Brandenberger et al. (*J Cell Biol* 2001 Jul 23;154(2):447-58).

The Examiner quoted Brandenberger et al. as stating "[w]hatever the mechanism, further investigations using [nephronectin] should advance our understanding of the puzzling function of $\alpha 8\beta 1$ in kidney development" (p. 456, right column, middle). However, this statement by Brandenberger et al. relates to the mechanisms by which nephronectin functions in conjunction with $\alpha 8\beta 1$ and by which $\alpha 8\beta 1$ functions in kidney development. It is well-established that an understanding of the mechanism by which an invention operates does not determine patentability. Furthermore, it is not uncommon in the field of biology for mechanisms by which something works to not be well-understood. For example, even though a pharmaceutical compound may be effective for treating a particular disease, the mechanism by which this pharmaceutical compound works may not be well understood. A lack of understanding of the mechanism by which the compound works would not affect patentability of the compound. The key to the utility of the compound is the end result, not the mechanism by which the compound achieves this result. Furthermore, even if a putative mechanism of action is generally agreed upon, this mechanism typically can not be definitively proved with 100% certainty and thus may not actually be the true mechanism.

Thus, in the present context, although Brandenberger et al. indicate that the mechanism by which nephronectin functions in conjunction with $\alpha 8\beta 1$ may not be well understood, and the function of $\alpha 8\beta 1$ in kidney development may be puzzling, what is established is that $\alpha 8\beta 1$ does affect kidney development, and "results strongly suggest that nephronectin is a relevant ligand mediating $\alpha 8\beta 1$ function in the kidney" (p. 447 of Brandenberger et al., 2nd column of abstract).

For example, Brandenberger et al. state the following:

1) "The integrin $\alpha 8\beta 1$ has recently been shown to play a crucial role during early stages of kidney morphogenesis (Muller et al., 1997)." (p. 447, column 1)
2) "In mice homozygous for a mutation in the $\alpha 8$ gene, initial growth and branching of the ureter are severely impaired. Thus the presence of $\alpha 8\beta 1$ promotes the development of the ureteric bud in a non-cell-autonomous manner." (p. 447, column 1)

3) "The epithelial-mesenchymal interactions required for kidney organogenesis are disrupted in mice lacking the integrin $\alpha 8\beta 1$ (p. 447, 1st sentence of abstract)

4) "Based on [the findings of Brandenberger et al], [Brandenberger et al.] suggest that nephronectin is a ligand in the kidney that mediates $\alpha 8\beta 1$ function during development. (p. 448, column 1, last sentence of the 1st full paragraph)

5) "...the distribution of nephronectin in the developing kidney appears to be essentially identical to that of the ligand(s) detected by $\alpha 8\beta 1$-AP, and nephronectin is clearly the major protein detected in blots of embryonic kidney extracts using $\alpha 8\beta 1$-AP. It is unusual for an integrin to remain associated with its ligand after immunoprecipitation, so the association of nephronectin with $\alpha 8\beta 1$ in immunoprecipitation suggests that these two proteins are associated in vivo. For this reason, it seems very likely to be a critical ligand in the signaling pathway in early metanephritic kidney development that was revealed by the phenotype of mice lacking $\alpha 8\beta 1$." (p. 456, 1st column, 2nd full paragraph).

Thus, it is clear that nephronectins have been specifically linked to specific aspects of kidney development, and therefore the skilled artisan will recognize that the claimed invention has specific and substantial utilities related to developmental disorders, particularly developmental disorders of the kidney. Consequently, because the claimed invention is supported by patentable utilities, Applicants respectfully request that the rejection under 35 USC §101 be withdrawn.

Rejection of claims 25 and 27 under 35 USC §112, 2nd paragraph

The Examiner rejected claims 25 and 27 as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention due to the recitation of both of the terms "having" and "consisting of".

Applicants have hereby amended claims 25 and 27 for clarity, as indicated above.

Conclusions

By way of the above amendments, claims 25 and 27 have been amended. As such, claims 4, 8-9, and 24-37 remain pending. The amendments to the claims and specification add no new subject matter and their entry is respectfully requested.

In view of the above amendments and remarks, Applicants respectfully submit that the application and claims are in condition for allowance, and request that the Examiner reconsider and withdraw the rejections. If for any reason the Examiner finds the application other than in condition for allowance, the Examiner is invited to call the undersigned agent at (240) 453-3812 should the Examiner believe a telephone interview would advance prosecution of the application.

Respectfully submitted,

CELERA GENOMICS

Date: March 3, 2004

By: _____

Justin D. Karjala
Reg. No. 43,704

Celera Genomics Corporation
45 West Gude Drive, C2-4#20
Rockville, MD 20850
Tel: 240-453-3812
Fax: 240-453-3084